UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,517	02/10/2000	MARCOS DA SILVA FREIRE	3673-2	6833

7590 09/15/2005

NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,517	DA SILVA FREIRE ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *97-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *97-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S-od

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6-27-2005 has been entered.

The amendment filed on 1-11-2005 is acknowledged. Claims 71-80 and 82-96 have been canceled. Claims 97-112 have been added. Claims 97-112 are pending and currently under examination.

Drawings

The drawings filed on 11-10-1999 are objected to as one cannot discern the data Figures 3A-C are meant to convey.

Claim Rejections Withdrawn

The rejection of claims 71-80 and 82-96 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a vaccine composition comprising propagating Yellow Fever Virus YF17D in chick embryo fibroblasts, does not reasonably provide enablement for methods producing a human vaccine comprising the propagation of any flavivirus other than YF17D on any cell type other than chick embryo fibroblasts is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (b) of the claimed method is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (d) of the claimed method is withdrawn. Cancellation of said claims has rendered the rejection moot.

New Grounds of Rejection - Enablement

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-103 and 105-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a human vaccine composition comprising propagating Yellow Fever Virus YF17D in chick embryo fibroblasts, does not reasonably provide enablement for methods producing a human vaccine comprising the propagation of any virus other than YF17D for the reasons set forth in the previous Office action in the rejection of 71-80 and 82-96. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth

below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the applicable factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

The instant claims are drawn to methods of producing a human vaccine comprising the propagation of a virus in permissive chick embryo fibroblast cells wherein said cells are initially seeded at a density of less than $2x10^5$ cells/cm^2 and infected with the seed virus at a multiplicity of infection (MOI) of 0.2-0.0001 infectious units per cell. However, the specification provides no guidance as to which virus and cell type other than YF17D and chick embryo fibroblasts could be used in the claimed methods. Moreover, the specification is silent on which viruses are able to infect chick embryo fibroblasts at the claimed MOI. Many viruses (e.g. influenza viruses) cannot be establish stable infections in permissive cells *in vitro* regardless of the MOI used and therefore said cultures are incapable of producing vaccine compositions comprising the infective

virus. While the specification provides a single working example in which chick embryo fibroblasts are infected with YF17D, it provides no guidelines for extrapolating said working example for use with any other virus or any other cell type. The specification does not provide guidance as to what the cell density should be at the time of infection nor does it provide any guidance as to how the claimed method needs to be adapted for the varying growth rates of differing cell types encompassed by the instant claims. Moreover, as pointed out by Applicant, the prior art would lead one of ordinary skill in the art to use higher cell densities and multiplicities of infection than those used in the claimed methods. While the skill level in arts of cell biology and virology is high, one of ordinary skill in the art would not be able to predict which viruses could be used with a given cell type to produce a productive infection resulting in the production of a human vaccine composition utilizing the MOI and cell densities claimed without undue experimentation. Therefore, given the lack of success in the art, the lack of working examples, and the unpredictability of the generation of a productive viral infection in a given cell type, the specification, as filed, is not enabling for methods producing a human vaccine comprising the propagation of any virus other than YF17D on any cell other than chick embryo fibroblasts.

It should be noted that Applicant argues that the rejected claims recite subject matter acknowledged by the Examiner as being enabled by the instant disclosure. Contrary to Applicant's assertion, the instant claims are not limited to the production of Yellow Fever Virus YF17D in chick embryo fibroblasts. Hence, the specification does not provide enablement for the full scope of the rejected claims for the reasons set forth previously and above.

New Matter

Claims 97-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claims 97 and 105 to recite "(c) incubating the cell culture obtained in step (b) at 30 to 40°C for a period of time between 12 and 144 hours...". Support for the limitation "12 to 144 hours" with regard to step (c) does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter. It should be noted that the disclosure of specific limitations, in specific examples, cannot be lifted from said examples and included in more generic method claims i.e. specific disclosures do not necessarily provide support for generic claim limitations.

Applicant has amended claim 100 to recite "incubating any of any of steps (c), (e), (g) and (i) is individually conducted for periods of time between 12 and 72 hours...". Support for the limitation "12 to 72 hours" with regard to step (c) does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter. It should be noted that the disclosure of specific limitations, in specific examples, cannot be lifted from said examples and included in more generic method claims i.e. specific disclosures do not necessarily provide support for generic claim limitations.

Applicant has amended claim 108 to recite "incubating of any of steps (c), (e), (g) and (i) is individually conducted for periods of time between 16 and 72 hours...". Support for the limitation "16 to 72 hours" with regard to any of the aforementioned steps does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter. It should be noted that the disclosure of specific limitations, in specific examples, cannot be lifted from said examples and included in more generic method claims i.e. specific disclosures do not necessarily provide support for generic claim limitations.

Applicant has amended claims 97 and 105 to recite "maintenance medium". Support for this limitation in the context of the claimed method does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter. It should be noted that the disclosure of specific limitations, in specific examples, cannot be lifted from said examples and included in more generic method claims i.e. specific disclosures do not necessarily provide support for generic claim limitations.

Applicant has amended claims 97 and 105 to recite, "(l) optionally, virally inactivating any non-attenuated virus...". Support for this limitation does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter.

Applicant has amended claim 102 to recite "and mixtures of at least two of human serum albumin, a peptide, an amino acid and a protein.". Support for this limitation does not appear in

the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Therefore this limitation is new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 97 and 105 are rendered vague and indefinite by the use of the phrase "virally inactivating any non-attenuated virus". It is unclear how one would inactivate only the non-attenuated viruses in the harvested supernatant. Moreover, it is unclear how one "virally" inactivates a virus. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claims 97 and 105 are rejected under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (b) of the claimed method is maintained for reasons set forth in the previous Office action in the rejection of claims 71 and 85. Contrary to Applicant's assertion, the amendment to the claims is insufficient to obviate this rejection. The units **cells/cm^2** are used to describe cell densities of adherent cell cultures, whereas cells/ml are the units used for suspension cultures. Consequently it is unclear how the claimed cell density of "less than $2x10^5$ cells/cm^2" applies to cultures. It should be noted that amended dependent claims 75-76 and 89 also recite this language.

Claims 97 and 105 are rejected under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (d) of the claimed method is maintained for the reasons set forth in the previous Office action in the rejection of claims 71 and 85. The amendment to said claims is insufficient to overcome the rejection. The method claims, as amended are confusing. If the cells are in a suspension culture, removing the medium also removes the cells (a separation step is lacking). Moreover, the cell "collection" of step (d) is never refed with culture medium and hence would not be able to survive 144 hours. Moreover, step (f) makes no sense since there is no culture medium to remove from the second incubated cell culture (all culture medium was removed in step (d). Additionally, it should be noted that while step (d) recites the inoculation of the claimed cells with 0.2-0.0001 infectious units per cell, it is unclear what the cell density of the culture is when infected.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman

ROBERT A. ZEMAN
PRIMARY EXAMINER

September 9, 2005